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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/424,244	04/11/2000	ANDREAS STRAUSS	P64075USO	7733

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EXAMINER	
HINES, JANA A	
ART UNIT	PAPER NUMBER
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/424,244	STRAUSS ET AL.	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. The amendment filed January 17, 2007 has been entered. Claims 1-14 have been cancelled. Claims 15-29 have been newly added. Claims 15-29 are under consideration in this office action.

Withdrawal of Rejections

2. The following rejections have been withdrawn in view of applicants' amendments and arguments:

a) The rejection of claims 1-1.4 under 35 U.S.C. 1-1-2, second paragraph;

b) The rejection of claims 1-2, 5, 9-11 and 14 under 35 U.S.C. 102(b) as being anticipated by
Samuelson (J. Bact., 1995);

c) The rejection of claims 3-4, 6, 12 and 13 under 35 U.S.C. 103(a) as being unpatentable over Samuelson (J. Bact., 1995) in view of Schneewind (Science, 1995); and

d) The rejection of claims 7 and 8 under 35 U.S.C. 103(a) as being unpatentable over Samuelson (J. Bact., 1995) in view of Schneewind (Science, 1995) in further view of Strauss et al.

New Grounds of Objection and Rejection

Claim Objections

3. Claims 16, 17, 19 and 20 are objected to because of the following informalities:

a) Claim 16 recites "emzymatic". Appropriate correction is required.

b) Claim 17 recites " is effected to the murein". Words appear to be missing from the sentence. Appropriate correction is required.

c) Claim 19 recites "Gram-positive bacterial" instead of "bacteria". Appropriate correction is required.

d) Claim 20 recites "The method according to characterized". The claim fails to recite the appropriate dependency. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 15-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) The preamble of the claims is drawn to a method for identifying active substances, however the recited steps within the method comprises a provision step, a contacting step, an assaying step and a correlation step. However the correlation step does not identify the active substances. Therefore, the goal of the preamble is not commensurate with the steps of the method that are drawn to identifying active substances.

b) Claim 17 recites the limitations "the murein" and "the cell wall" in the claim. There is insufficient antecedent basis for these limitations in the claim. Therefore appropriate clarification is required to overcome the rejection.

c) Regarding claim 23, the phrase "vice versa" renders the claim indefinite because the meets and bounds of the phrase are unclear. Appropriate clarification is required to overcome the rejections.

d) The phrases "low natural cell wall turnover" "a small number" in the claim are relative phrases that render the claim indefinite. The phrases are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of how low the natural cell wall turnover needs to be or how small the number of proteases needed is unclear. There is no comparison value for which one could use to determine a low turnover or a small number. Therefore appropriate clarification is required to overcome the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 15-16, 20, 24-26 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Samuelson (J. Bact., 1995).

The claims are drawn to a method for identifying active substances which affect the covalent bonding of polypeptides to the surface of Gram-positive bacteria, comprising the following steps: a) providing a sample of Gram-positive bacteria which

contain or produce at least one enzymatic reporter substances which is or can become covalently bonded to the surface of the Gram-positive bacteria, said at least one reporter substance having a different enzymatic activity when not covalently bonded to the surface of the Gram-positive bacteria from that exhibited when it is covalently bonded to the surface of the Gram-positive bacteria; b) contacting the sample with a possible active substance; c) assaying the enzymatic activity of the reporter substance of the Gram-positive bacteria of the correlating the enzymatic activity of the reporter substance to a capability of the active substance to affect the covalent bonding of polypeptides to the surface of gram-positive bacteria. The dependent claims are drawn to the assaying of enzymatic activity, the hybrid polypeptide, the linker peptide, the gram-positive bacteria, and the reporter substances.

Samuelson (J. Bact., 1995) teaches cell surface display of recombinant proteins on *Staphylococcus carnosus.* Surface display of heterologous proteins on bacterial cells is an important objective for many applications in microbiology and molecular biology (page 1470). The use of enzyme-coated bacteria as novel biocatalyst has been envisioned because enzymes with retained activity have been surface displayed on E. coli cells (page 1470). Investigations with gram-positive bacteria for cell surface display of has been initiated (page1470). The surface receptors of gram positive bacteria seem to be more permissive for the insertion of extended sequences of foreign proteins then do the different gram-negative systems (page 1470). Gram-positive bacteria have the additional advantage of being more rigid because of the thicker cell wall, thus making it possible to use the intact bacteria for separation purposes (page 1470). A 198 amino

acid region, designated ABP (albumin binding protein) was expressed adjacent to the cell wall to increase accessibility to the surface-displayed target peptides (page 1471).

The Materials and Methods section teaches enzymatic assay for the detection of recombinant surface displayed receptors (page 1471) and immunofluorescence assay for detection of peptides on the cell surface (page 1472). The method teaches contacting the sample and using a fluorescence activated cell sorter to analysis the bacteria (page 1472). The colorimetric assay for detection used strep avidin-alkaline phosphatase to detect a color change (page 1473). Recombinant and wild-type *S. carnosus* cells were grown and subjected to the enzymatic assay, performed in an ELISA plate format, wherein a positive color response was found for the cultivation harboring plasmids (page 1473). See Figure 3 which compares the wild type to the cultivations harboring plasmids. This demonstrates that hybrid receptors with serum albumin binding capacity were accessible on the cell surface (page 1474). For cell surface binding, anchoring regions were investigated (page 1475).

There is a charged repetitive region postulated to interact with the peptidoglycan cell wall and a region common for gram-positive cell surface bound receptors containing an LPXTGX motif, a C-terminal hydrophobic region and a charged tail (page 1475). It has been demonstrated that all three regions are required for cell surface anchoring and that the cell sorting is accompanied by proteolytic cleavage at the C-terminus and covalent linking of the surface receptor to the cell wall (page 1475). Finally, flow cytometry was successfully employed and a fluorescence-labeled secondary antibody

and a primary antibody reactive with the ABP region of the hybrid receptors could be used to stain the cells (page 1475).

Therefore, Samuelson (J. Bact., 1995) teaches a method for identifying active substances on the surface of gram-positive bacteria comprising: provision step; a contact step, an assaying step and a correlation step.

Response to Arguments

Applicants' urge that Samuelson does not detect the gram-positive bacteria using antibody or enzymatic binding assays. However In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies i.e., Antibody or enzymatic binding assays are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants' also urge that Samuelson does not teach a method for identifying active substances which affect the covalent bonding of polypeptides to the surface of the gram-positive bacteria. In response to applicant's arguments, the recitation of a method for identifying active substances which affect the covalent bonding of polypeptides to the surface of the gram-positive bacteria has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the

preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). Furthermore the claims only require the provision of an enzymatic reporter substances which is or can be covalently bonded to the surface of the Gram-positive bacteria which the art teaches. Therefore Samuelson teaches the limitations of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 18-19, 21, 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Samuelson (J. Bact., 1995) in view of Schneewind (Science, 1995).

The claims are drawn to a method for identifying active substances which affect the covalent bonding of polypeptides to the surface of Gram-positive bacteria, comprising the following steps: a) providing a sample of Gram-positive bacteria which contain or produce at least one enzymatic reporter substances which is or can become covalently bonded to the surface of the Gram-positive bacteria, said at least one reporter substance having a different enzymatic activity when not covalently bonded to the surface of the Gram-positive bacteria from that exhibited when it is covalently bonded to the surface of the Gram-positive bacteria; b) contacting the sample with a

possible active substance; c) assaying the enzymatic activity of the reporter substance of the Gram-positive bacteria of the correlating the enzymatic activity of the reporter substance to a capability of the active substance to affect the covalent bonding of polypeptides to the surface of gram-positive bacteria. The claim are drawn to the interpeptide bridges, the pathogenicity factors, the hybrid polypeptide, the expression of lyostaphin immunity factor and the reporter substances.

Samuelson (J. Bact., 1995) has been discussed however, Samuelson (J. Bact., 1995) does not teach the cell wall structure and hybrids polypeptide succession.

Schneewind (Science, 1995) teaches structure of the cell wall anchor of surface proteins in *Staphylococcus aureus*. Many surface proteins are anchored to the cell wall of gram-positive bacteria and are involved in the pathogenesis of these organisms (abstract). A hybrid molecule was designed and when expressed is anchored to the cell wall and can be released by controlled enzymatic digestion (abstract). By a combination of molecular biology and mass spectroscopy techniques, the structure of the cell wall anchor of surface proteins was revealed (abstract). Alter cleavage of surface proteins between threonine and glycine of the conserved LPXTG motif, the carboxyl of threonine is amide linked to the free amino group of the pentaglycine cross bridge in the staphylococcal cell wall (abstract). The N-terminal immunoglobulin-binding domains of protein A are displayed on the cell surface, whereas the C-terminal end is anchored to the bacterial cell wall (page 103). This ability to anchor to the cell wall requires a 35 residue sorting signal that is located at the predicted C-terminus of protein A and consists of an LPXTG motif, followed by a C-terminal hydrophobic domain and a tail of

mostly positively charged residues (page 103). Cell wall anchored molecules of gram positive bacteria have similar topologies in that the N-terminal domain is displayed on the cell surface, whereas the C-terminal anchor structure is buried in the thick peptidoglycan layer (page 103). The pentaglycine peptide, lysostaphin cleaves randomly between any of the four glycyl-glycine peptide bonds (page 105). The lysostaphin cleavage occurred between the third and fourth glycine of the pentaglycine cross bridge, selectivity which could be the result of the stearic hindrance imposed by the anchored protein and the linked cell wall peptide (page 105). Surface proteins are exported by a means of an N-terminal signal/leader sequence (page 105), See figure 4A and 4B. The release of peptidoglycan fragments with linked surface proteins in gram-positive bacteria may be caused by physiological turnover and the enzyme responsible may represent a novel target for antibacterial therapy (page 105).

Therefore, it would have been obvious at the time of applicants invention to modify the method of Samuelson (J. Bact., 1995) with polypeptides which effect the cell wall, pathogenicity, use linker peptides and teach cell wall exchange as taught by Schneewind (Science, 1995), because Schneewind (Science, 1995) teaches that such modification are drawn to the structure of the cell wall anchor of surface proteins and designed an expressed hybrid molecule requires no more than routine skill. One of skill in the art would have been motivated to make such modifications because Schneewind teaches hybrid molecule can be released by controlled enzymatic activity. Furthermore no more than routine skill would have been required to incorporate such modifications when the art teaches novel targets for antibacterial therapy found by the release of

peptidoglycan in gram-positive bacteria may be caused by physiological turnover and the responsible enzyme.

Response to Arguments

Applicants' argue that neither Sameulson nor Schneewind teach a method in which at least one reporter substance has a different enzymatic activity when not covalently bound to the gram-positive bacteria. Applicants' argue that neither reference teaches the search for active substances like anti-infectives affecting the covalent bonding pf polypeptides on the surface of the bacteria. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (.e., the search for active substances like anti-infectives are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The art teaches that enzymatic activity is affected by physiological turnover and the enzyme responsible may represent a novel target for antibacterial therapy, furthermore the art teaches that covalent bonds affective the activity of the polypeptides contrary to applicants arguments. Furthermore, there is no limitation in any can which is drawn to such, therefore applicants' argument is not persuasive and the rejection is maintained.

7. Claims 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Samuelson (J. Bact., 1995) in view of Schneewind (Science, 1995) in further view of Strauss et al.

The claims are drawn to a method for identifying active substances which affect the covalent bonding of polypeptides to the surface of Gram-positive bacteria, comprising the following steps: a) providing a sample of Gram-positive bacteria which contain or produce at least one enzymatic reporter substances which is or can become covalently bonded to the surface of the Gram-positive bacteria, said at least one reporter substance having a different enzymatic activity when not covalently bonded to the surface of the Gram-positive bacteria from that exhibited when it is covalently bonded to the surface of the Gram-positive bacteria; b) contacting the sample with a possible active substance; c) assaying the enzymatic activity of the reporter substance of the Gram-positive bacteria of the correlating the enzymatic activity of the reporter substance to a capability of the active substance to affect the covalent bonding of polypeptides to the surface of gram-positive bacteria. The claims are drawn to the hybrid polypeptide, and a proenzyme.

Samuelson (J. Bact., 1995) and Schneewind have been discussed however, neither does not teach the enzyme being a proenzyme.

Strauss et al., teaches *in vivo* immobilization of enzymatically active polypeptides on the cell surface of *Staphylococcus carnosus*. Many surface proteins of gram-positive bacteria are covalently anchored to the cell wall by ubiquitous mechanisms, involving a specific, C-terminal sorting signal (abstract). To achieve cell wall immobilization of a

normally secreted enzyme in vivo, the authors constructed a hybrid protein consisting of Staphylococcus hyicus lipase and *S.aureus* fibronectin binding protein B (abstract). The lipase is a pre-proenzyme (page 492). Expression of the hybrid protein in *S. carnosus* resulted in efficient cell-wall anchoring of enzymatically active lipases (abstract). The cell wall lipase retained more than 80% of the specific activity as compared to unmodified lipase (abstract). When the lipase was replaced by another enzyme, the resulting hybrid was also efficiently anchored in an active conformation to the cell wall of the bacteria (abstract). The results demonstrate that it is possible to immobilize normally soluble enzymes on the cell wall of *S. carnosus*, without radically altering their catalytic activity, by fusing them to a cell wall immobilization unit, consisting of a suitable cell wall spanning region and a standard cell wall sorting signal (abstract).

Therefore, it would have been obvious at the time of applicants' invention to modify the method of Samuelson (J. Bact., 1995) and Schneewind because Strauss et al., teach that proenzymes are usable with the well known method of identifying substances which affect the covalent bonding of polypeptides to the surface of gram-positive bacteria. One of skill in the art would have been motivated to make such modifications because Strauss et al., teach cell wall immobilization and the construction of a hybrid protein, just as taught by Samuelson (J. Bact., 1995) and Schneewind; therefore no more than routine skill would have been required to use an alternative functionally equivalent hybrid in a well known method of identification. Furthermore, no more than routine skill would have been required to use of proenzyme and determine the change in enzymatic activity when the art teaches that changes in enzymatic activity

can occur without radically altering their catalytic activity thereby making them useful in said methods of identification.

Sequence Compliance

8. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth in the Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. The specification and claim 21 refer to sequence "LPXTG" however the sequence must be identified with a sequence identifying number.

Conclusion

9. No claims allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Jeffery Siew, can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines
March 31, 2007

MARK NAVARRO
PRIMARY EXAMINER